EXHIBIT 3

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Paper No.____

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

CENTOCOR, INC.,
Junior Party
(U.S. Application 10/912,994)

v.

ABBOTT GMBH & CO., KG,
Senior Party
(U.S. Patent 6,914,128)
Patent Interference No. 105,592 (McK)
(Technology Center 1600)

ABBOTT TUTORIAL

I. BACKGROUND

On May 1, 2009, the Board invited Abbott and Centocor to file a "tutorial" educating the Board on the subject matter involved in Count 1 and the involved claim 1 of both parties. As requested by the Board, Party Abbott has attempted to minimize, to the extent possible, the use of technical biotechnology terms.

The tutorial materials set forth below are provided solely for the purposes of facilitating understanding of the biotechnology involved in the present interference and are not to be construed in any way as a substitution for or a scientific characterization of the technology discussed.

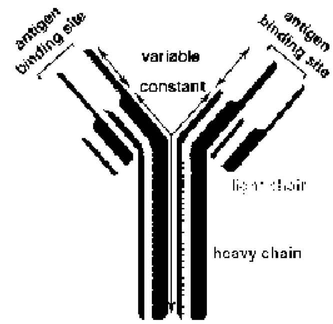
II. ANTIBODIES, ANTIGENS AND IMMUNITY

The immune system is the body's defense against diseases caused by invading microorganisms and other foreign substances. Antibodies are a key part of a healthy immune system. The term antibody refers to a class of proteins (also generally called "Immunoglobulins" or "mAbs" or "Igs", generally known to encompass "Fvs" and "scFvs"). An antibody is a protein typically produced in response to invasion by a foreign substance. Antibodies function within the immune system of an animal to bind to, and, to remove substances in the body. These foreign substances can be anything from viruses to bacteria to essentially any other molecule that is not made by the body. These foreign substances are known broadly as "anti-gen-s" for antibody generating substances.

When the immune system recognizes an antigen, it signals a particular type of cell known as a B cell to produce an antibody to that antigen. The newly produced antibody is then released into the blood stream. When the antibody comes in contact with its antigen, they bind together. The presence of the antibody on the antigen enables various immune system cells to locate the antigen and either destroy it or move it to where it can be expelled from the body.

A. Antibody Structure

Antibodies are proteins that are made from four chains of amino acids (the building blocks of all proteins). There are two identical pairs of chains, a “heavy” pair and a “light” pair. This means that, generally, an antibody consists of a total of four amino acid chains – two heavy chains and two light chains joined to form a "Y" shaped molecule, as shown below.



The two heavy chains (colored blue, above) make up a stock and one arm for the Y. The light chains (colored red, above) overlap the heavy chains on the arms of the Y. Each of these four chains can be further broken down into regions, called “variable” regions and “constant” regions.

The variable regions of an antibody molecule (critical components of an antibody that are sometimes abbreviated “scFvs”) are located within the arms of the Y structure. This is the location of the antigen binding sites – where the antibody binds to its antigen. The stock of the Y is constant and does not bind to antigen.

1. The Variable Domains of An Antibody Molecule Confer Specificity of an Antibody to a Particular Antigen

The variable domains of an antibody are the sites where an antibody binds to antigen and vary significantly from one antibody to the next. Although the variable domain of the Light Chain is different from the variable domain of the Heavy Chain, they share some structural similarities. Each variable domain is composed of a set of three "Hypervariable regions" referred

to as Complementarity Determining Regions, or CDR's. It is the CDR set of the Variable Domain that confers the antigen binding specificity and "affinity" of the antibody.

Although generally all antibodies have variable regions, the variation present in the variable regions allows some antibodies to bind antigen more strongly than others. Antibody-antigen binding is a *dynamic* process, which means that an antibody does not simply stick to an antigen. Rather, an antibody and antigen bind tightly and then release – a process that occurs over and over again. The most common term used to describe the degree of binding and releasing of an antibody to an antigen is called "affinity." Affinity refers to the strength of antibody-antigen binding.

Antibody affinity can be determined empirically (i.e., assigned a specific numerical value). One conventional expression of antibody affinity is "Dissociation Constant" (abbreviated K_D) which is a number reflecting the rate an antibody is releasing (K_{off}) an antigen compared to the rate of binding (K_{on}) an antigen. The smaller the dissociation constant, the tighter an antibody binds.

Tight binding antibodies are high affinity antibodies whereas loose binding antibodies are low affinity antibodies. Typically, tight binding or high affinity antibodies provide the most utility.

2. The Constant Regions of Antibodies Don't Vary Much Within Species

The constant regions of the antibody are located on the stock and the lower portions of the arms of the Y. These constant regions interact with cells in the body's immune system once the antibody has attached to the targeted antigen. Within any given species, such as mice, the composition of the constant region is generally the same from one antibody to another. However, constant regions are different from one species to another (mouse versus human constant regions are very different).

B. Antigens, Such as IL-12

As mentioned before, an antigen is a substance that when introduced into a foreign host typically gives rise to an immune response. The present interference involves the antigen human IL-12. Interleukin 12 (abbreviated IL-12) is one of several proteins of a class of proteins (collectively referred to as "cytokines"). Cytokines act to signal different cells in the body.

Human IL-12 is made by humans, and is therefore present in the human body normally. IL-12 is secreted by immune cells during some types of immune responses. Human IL-12 is referred to as a “self-antigen” at times, because it is made by humans. IL-12 is a heterodimeric (i.e., composed of two different and separate protein subunits) 70 kDa[1] glycoprotein (commonly called IL12-p70). It is *hetero*dimeric because it consists of two *different* subunits, namely a 40 kDa subunit (commonly called “p40”) and a 35 kDa subunit (commonly called “p35”) which are linked via chemical bonds. Antibodies can bind to a specific subunit of IL-12 (the p40 subunit) but not bind to the other subunit (the p35 subunit), or *vice versa*.

IL-12 can influence human biology, including disease development and progression. One major role of IL-12 signaling is in inflammation. Under normal conditions, cytokines perform useful and protective bodily functions. If however, a cytokine such as IL-12 is deregulated (e.g., overproduced) signaling is disrupted, which can result in a variety of human disorders. Thus, antibodies to IL-12 can be used to treat IL-12 mediated disease because the antibody can bind IL-12 and reduce IL-12 activity.

C. Sources and Types of Antibodies

1. Non-Human (i.e., Mouse) Antibodies

The human immune system will not normally make antibodies to its own cells or its own proteins (i.e., it will not attack itself). One technique for producing antibodies to human proteins is to get an animal to make the antibodies and then administer those non-human antibodies to a

[1] kDa means the mass of the molecule.

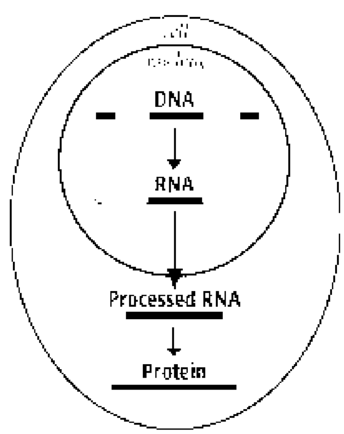
human. In this technique, a protein is taken from a human and injected into a non-human, such as a mouse. The mouse recognizes the human protein as a foreign invader and produces antibodies to the human protein. Antibodies capable of binding to the human protein can then be isolated from the mouse. Such antibodies removed from a mouse are non-human antibodies because the source (i.e., a mouse) was a non-human. Mouse antibodies are also called "rodent" and "murine" antibodies. Non-human (e.g., murine) antibodies can then be administered to a human and can alter the activity of the human protein to which the antibodies bind (including neutralizing or enhancing the human protein's activity). Making antibodies in non-humans has been known for many decades.

But the usefulness of introducing non-human antibodies in humans is limited because the antibodies created by non-humans, such as mice, are recognized as foreign when introduced into the human body. The non-human antibodies are then attacked by the human's immune system. In the case of introducing mouse antibodies into a human, this reaction is known as the <u>h</u>uman <u>a</u>nti-<u>m</u>ouse <u>a</u>ntibody response or HAMA response. As a result, mouse antibodies will only be effective in a human for the short time prior to attack by the human immune system. If non-human antibodies are continually administered to a human, there is a risk for a potentially serious life-threatening reaction.

A solution to avoid adverse responses to injected non-human antibodies in humans is to inject *human* antibodies into a human instead of non-human antibodies. But, obtaining appropriate human antibodies is exceptionally difficult. Unfortunately, immunizing a human with a human protein is not effective at generating antibodies, because the human immune system won't normally recognize human proteins as "foreign" invaders and because humans <u>cannot</u> be used experimentally to inject with antigens to produce antibodies, like mice can.

One potential solution to this problem was to genetically engineer antibodies to include a reduced amount of mouse material. Genetic engineering is the process of creating new genes or

genetic combinations (i.e., DNAs) or new proteins or protein combinations to make something that may not occur in nature. DNA carries the genetic information of a cell and consists of thousands of genes, including genes for making antibodies. Each gene serves as a recipe on how to build a protein molecule. The flow of information from the genes determines protein composition. DNA is located in the nucleus of cells (i.e., in chromosomes). When proteins are needed by a cell, the corresponding genes in the DNA are transcribed into a molecule called RNA, which is in some ways similar to DNA in that it also provides instructions on making a protein. The RNA is further processed by the cell and is then transported out of the nucleus of the cell. Outside the nucleus, the proteins are assembled based upon the instructions in the RNA. This process is illustrated below.



For decades, using insights into the ways in which cells naturally make proteins, scientists have been able to remove DNA from a cell, manipulate the DNA and then introduce the altered DNA into new cells (or viruses) in order to make proteins that do not exist in nature. This process is useful in making engineered antibodies.

Manipulation of DNA includes joining together pieces of the DNA of one species (i.e., a mouse) to DNA from another species (i.e., a human). The resulting DNA contains biological instructions to make proteins, such as new antibodies, that do not occur in nature. Once created, the new DNA can be inserted into cells or viruses which will then make the material of interest

(e.g., a part-mouse part-human antibody). Scientists first began to use recombinant DNA technology in the mid-1980's to enable the creation of *partially* human antibodies. These engineered antibodies can possibly somewhat reduce the problems associated with using antibodies from other species to treat human diseases (i.e., HAMA responses). One type of antibody created by genetic engineering is the chimeric antibody.

2. Chimeric Antibodies

Chimeric antibodies, which first became known in 1984, use genetic engineering to combine parts of antibodies from different species of animals. The name "chimeric" comes from the chimera, the animal in Greek mythology that was part lion, part goat and part snake. A chimeric antibody is constructed by starting with a non-human (i.e., mouse) monoclonal antibody and substituting a human constant region for the mouse constant region.

Antibodies of this kind are not found in nature. The use of a human constant region (the stock of the Y shape described earlier) can, to a limited degree, potentially avoid triggering or exacerbating adverse reactions to non-human antibodies administered to a human, even if the variable region (the arms of the Y shape described earlier) is from a mouse. As a result, chimeric antibodies potentially are less likely to be attacked by the human immune system and the possibility of human anti-mouse antibody response is reduced. This sometimes allows for multiple treatments using the chimeric antibody.

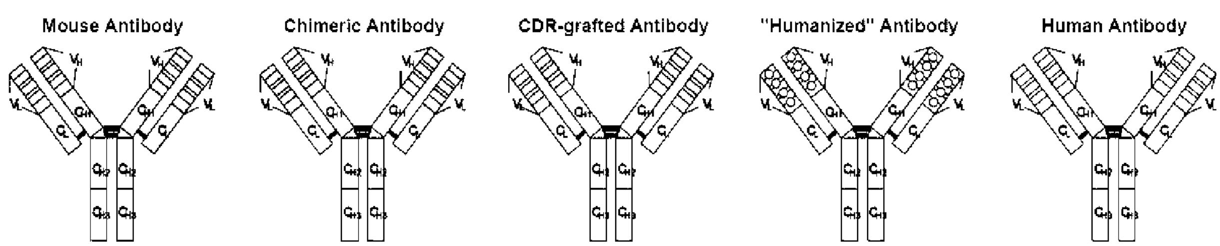
3. **Humanized Antibodies**

After chimeric antibodies were developed, scientists developed a new type of antibody called a humanized antibody, which is an antibody that has more human material than the ordinary chimeric mouse-human antibody. Humanized antibodies are antibodies with a mouse component. Typically, the mouse portions of a humanized antibody are the portions of the antibody important for binding to the antigen (or CDRs). Remember that the CDRs are the antigen binding sites on the antibody that are important for contacting the antigen. To make a

humanized antibody, human variable and human constant regions are linked to CDRs from a mouse monoclonal antibody known to bind the human antigen of interest. Humanized antibodies are sometimes called CDR grafted antibodies. Humanized antibodies are *not* human, as humanized antibodies are still part mouse and <u>not</u> fully human. Nonetheless, because most of the antibody is human, the possibility of human anti-mouse antibody response or HAMA response is sometimes reduced, but a risk of a HAMA response still exists.

4. **Human Antibodies**

Finally, after decades of work, a human antibody that binds to a human antigen was developed. Unlike all antibodies before it, including mouse, chimeric and humanized antibodies, human antibodies are made from scratch in a laboratory and have <u>no</u> components derived from mice or other non-human species. Because no non-human genes are used to derive these antibodies, there is no risk of a HAMA response. The very first fully human therapeutic antibody developed was Humira™, made by Abbott, discovered by a team of scientists at Abbott, led by Dr. Jochen Salfeld. The advances in recombinant antibody technology and differences between the various antibodies we just discussed is illustrated below.



In the above illustration, yellow depicts non-human (i.e., mouse) material where as blue depicts human material. Note, the human antibody (depicted on the far right, above) contains <u>no</u> non-human material. Thus, mouse, chimeric and CDR-grafted, humanized and human antibodies are <u>distinct</u> types of antibodies produced using distinct methods.

D. Producing Human Antibodies - Phage Display Technology

The very first process used to make human antibodies is called phage display technology, a sophisticated and complex technique which operates, when properly used with other methods, similar to the way a human makes antibodies. This technology was developed by CAT (Cambridge Antibody Technology), and used by CAT and Abbott to obtain the first fully human antibody. Generally speaking, phage display technology permitted the creation of a vast "library" of human candidate antibodies in a single test tube. Phage display technology is a very useful tool for displaying each antibody member of the library, screening (or panning) each member of the library for binding (e.g., to IL-12), selection of a member of the library and further manipulations of the selected member.

In phage display, human tissues are first used to obtain human genetic starting materials (i.e., DNA pieces). The human donors are healthy. The human DNAs correspond to (i.e., code for) millions of potential antibodies. These DNAs are collectively referred to as a human DNA library. The DNAs are each then included inside of a bacteriophage virus - a virus (which in this context can be thought of as a vehicle for containing and moving DNA) that infects bacteria. The bacteriophage virus contains the DNAs, uses the DNAs to make the corresponding protein, and also shows or displays the protein (corresponding to each DNA contained inside) on its surface. In other words, when a DNA encoding an antibody protein is inside the virus the virus can display the antibody (or just the antigen binding portion or scFv) on its surface. Many, many bacteriopages can be grown in the laboratory, each displaying a different antibody. This process is depicted below.

Phage Library with
Antibodies on Surfaces

This is very useful because the virus can then be brought into contact (i.e., panned) with an antigen, such as IL-12, and the speicifc antibody among many millions in the library that binds to the specific antigen can thus be identified. Once a single phage containing and displaying the antibody of interest is selected, it can be used to obtain the corresponding antibody DNA inside it and human antibodies can be further produced using that DNA. The end result of the use of a phage display method is obtainment of a human antibody that binds to a specific antigen, such as IL-12.

It is particularly important to note that because the source antibody genetic material is *entirely* human, and because no DNA of any non-human species is ever involved in this process, scientists know that the antibodies isolated from the phage display library are human antibodies.

E. Determining The Biological Properties of An Antibody

1. Hybridoma Technology

In the mid-1970's, scientists developed a technique for making antibodies that are all identical to each other. These kinds of antibodies are known as *monoclonal* (also referred to as "isolated" or "purified") antibodies. Briefly, the technique used to make monoclonal antibodies is called the hybridoma technique and involves injecting human antigens into a mouse or other non-human, which in turn makes antibodies, each of which can be isolated. Monoclonal

technology allows for the production of antibody "clones" which have the same properties and bind the same target. But even with the invention of the hybridoma technique, the potential of administering non-human antibodies to humans was limited by a human's normal immune reaction to antibodies produced by other species, such as mice.

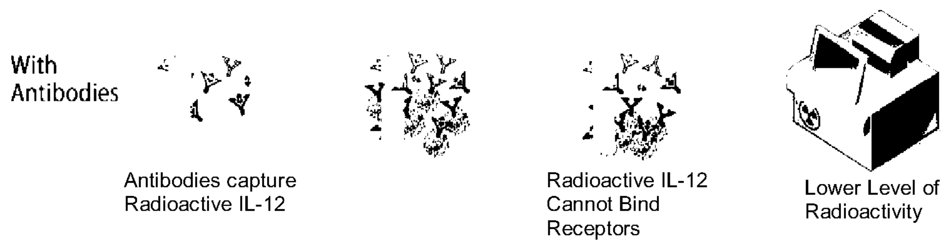
2. The Receptor Binding Neutralization Assay

Once an antibody is identified from a library it is important to determine the biological properties of the antibody. For example, some antibodies can induce reactions (i.e., enhance IL-12 activity thereby causing more inflammation) whereas some antibodies block reactions, even though the antibodies may bind to the same target. If one desires to administer an antibody to treat a disease caused by an antigen and one administers instead an antibody that induces the disease very harmful effects in humans could occur. One method to determine if an antigen inhibits or neutralizes an antigens' activity is commonly called a Receptor Binding Assay, or an RBA.

First, human cells are stimulated in a dish with a substance called PHA. PHA causes the human cells to express receptors on their surface (i.e., IL-12 receptors). The amount of IL-12 receptors on the surface of the stimulated cells can be determined by reacting the cells with radioactive IL-12. Once the radioactive IL-12 is bound to the IL-12 receptors on the cell surface, the excess radioactive IL-12 is washed away and the cells are counted in a radiation counter. The amount of radiation obtained represents the total amount of IL-12 that can bind, and is therefore a direct expression of how much IL-12 receptor is on the surface of the cells used in the assay.

ABT-IL12-01423065

In a separate dish, a human antibody to IL-12 may be included. If the human antibody to IL-12 neutralizes the binding of the radioactive IL-12 to the IL-12 receptor on the cell surface, the antibody-radioactive IL-12 complex will be washed away.

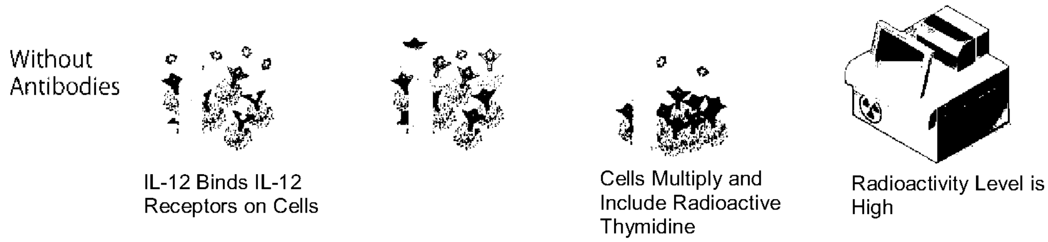


Then, when the cells are counted in a radiation counter, less radioactive IL-12 will be bound to the IL-12 receptors on the cells and the level of radioactivity will be lower. The reduction of binding that is detected indicates that there is inhibition or neutralization of IL-12, because IL-12 is unable to bind to the IL-12 receptor on the cell.

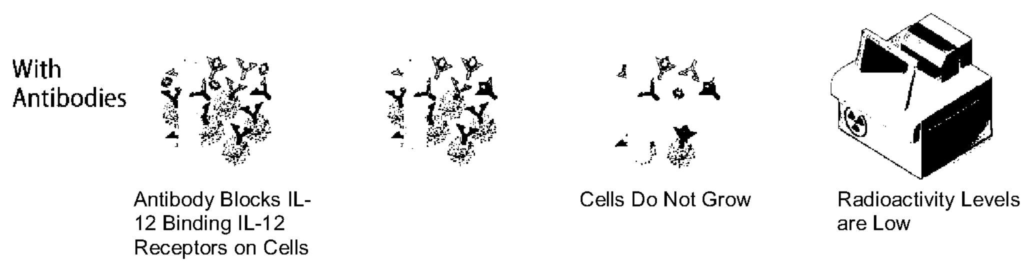
3. The PHA Blast Neutralization Assay

Another method to determine if an antigen inhibits or neutralizes an antigens' activity is commonly called a PHA blast assay. A PHA Assay analyzes the ability of an antibody to bind and neutralize IL-12 by inhibiting the proliferation of PHA stimulated human blast cells.

Like in the RBA discussed above, first, human cells are stimulated in a dish with a substance called PHA. PHA causes the human cells to express receptors on their surface (i.e., IL-12 receptors). Human IL-12 is then incubated in the presence of human cells and radioactive Thymidine, which incorporates itself into the DNA of dividing cells. If IL-12 binds to the receptors on the surface of the human cells, the cells divide. The incorporation of radioactive-Thymidine into cellular DNA of the PHA stimulated blast cells is measured in a radiation counter.



If an antibody to IL-12 is added to the dish, the antibody will block binding of IL-12 to the IL-12 receptor on the surface of the cell. This will then block the signal for the cell to grow. If the cell does not grow, the cell cannot incorporate the radioactive Thymidine into its cellular DNA and thus, the radioactivity of the cells in the dish will decrease.



If the incorporation of radioactive Thymidine into the DNA of PHA blast cells drops below the maximal response observed in the presence of IL-12 (i.e., where no antibody to IL-12 is present), the isolated human antibody bound to and neutralized human IL-12, thereby inhibiting PHA blast cell proliferation.

F. Overview of the Coordinated Processes Described Above To Make A Human Antibody to Human IL-12

The described processes (*inter alia*, phage display technology, receptor binding assay and PHA Blast Assay), when successfully coordinated and performed, can work in concert to obtain a human antibody to a human antigen, such as IL-12. This process involves successfully using human antibody libraries to isolate human antibodies for human IL-12 via "panning" (i.e., bringing the human IL-12 in contact with the library), using methods including Enzyme-Linked ImmunoSorbent Assays. The human antibodies that bind to the human IL-12 are then tested in

Receptor Binding Assays and PHA Assays to establish whether or not the chosen human antibodies neutralize human IL-12. The process is then repeated, typically requiring scientific judgments to be made in each step, in order to refine the human antibody, consistent with the way Abbott obtained numerous fully human antibodies that bind human IL-12 and neutralize human IL-12.

III. CONCLUSION

As requested by the Board, Party Abbott has attempted to describe, to the extent possible in plain language, biotechnology terms important in the present interference. If there remains any aspect of the technology the Board would like additional briefing on, or an alternative form of briefing (i.e., an animation) Party Abbott will provide additional information to the Board.

Respectfully submitted,

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CERTIFICATE OF FILING

The undersigned hereby certifies that a copy of the paper entitled **"ABBOTT TUTORIAL"** was filed on this 29th day of May, 2009, via Web Portal.

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the paper entitled **"ABBOTT TUTORIAL"** was served on this 29th day of May, 2009, by email on the Attorneys of Record for the party Centocor to the email addresses below:

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